α,ω-DICARBOXIMIDE DERIVATIVES AS USEFUL URO-SELECTIVE α_{1A} ADRENOCEPTOR BLOCKERS

FIELD OF THE INVENTION

This invention relates to certain novel α,ω-dicarboximide derivatives which selectively inhibit binding to the α_{1A} adrenergic receptor, a receptor which has been shown to be important in the treatment of benign prostatic hyperplasia. The compounds of the present invention are potentially useful in the treatment of benign prostatic hyperplasia. This invention also relates to methods for synthesizing the novel compounds, pharmaceutical compositions containing the compounds, methods of treating benign prostatic hyperplasia using the compounds, and intermediate compounds used in the preparation of novel compounds.

BACKGROUND OF THE INVENTION

Benign prostatic hyperplasia (BPH), a nonmalignant enlargement of the prostate, is the most common benign tumor in men. Approximately 50% of all men older than 65 years have some degree of BPH and a third of these men have clinical symptoms consistent with bladder outlet obstruction (Hieble and Caine, Fed. Proc., 1986; 45:2601). Worldwide benign and malignant diseases of the prostate are responsible for more surgery than diseases of any other organ in men over the age of fifty.

It is generally accepted that there are two components of BPH, a static and a dynamic component. The static component is due to enlargement of the prostate gland, which may result in compression of the urethra and obstruction to the flow of urine from the bladder. The dynamic component is due to increased smooth muscle tone of the bladder neck and the prostate itself (which interferes with emptying of the bladder) and is regulated by alpha 1 adrenergic receptors (α_1-ARs). The medical treatments available for BPH address these components to varying degrees, and the therapeutic choices are expanding.

Surgical treatment options address the static component of BPH and include transurethral resection of the prostate (TURP), open prostatectomy, balloon dilatation, hyperthermia, stents and laser ablation. Although, TURP is the gold standard treatment for patients with BPH, approximately 20-25% of patients do not have a satisfactory long - term outcome (Lepor and Rigaud, J. Urol., 1990; 143:533). Postoperative urinary tract infection (5-10%), some degree of urinary incontinence (2-4%), as also reoperation (15-20 %) (Wennberg *et al.*,JAMA, 1987; 257:933) are some of the other risk factors involved.

Apart from surgical approaches, there are some drug therapies which address the static component of this condition. Finasteride (Proscar, Merck), is one such therapy which is indicated for the treatment of symptomatic BPH. This drug is a competitive inhibitor of the enzyme 5α-reductase which is responsible for the conversion of testosterone to dihydrotestosterone in the prostate gland (Gormley *et al.*, N. Engl. J. Med., 1992; 327:1185). Dihydrotestosterone appears to be the major mitogen for prostate growth, and agents which inhibit 5-α-reductase reduce the size of the prostate and improve urine flow through the prostatic urethra. Although finasteride is a potent 5α-reductase inhibitor and causes a marked decrease in serum and tissue concentration of dihydrotestosterone, it is only moderately effective in treating symptomatic BPH (Oesterling, N.Engl.J.Med., 1995; 332:99). The effects of finasteride take 6-12 months to become evident and for many men the clinical improvement is minimal.

Due to the limited effectiveness of 5α-reductase inhibitors in terms of immediate symptomatic and urodynamic relief, other pharmacological approaches have been assessed in the clinical setting.

The dynamic component of BPH has been addressed by the use of adrenergic receptor blocking agents (α_1-AR blockers) which act by decreasing the smooth muscle tone within the prostate gland itself. α_1-adrenergic receptor antagonists appear to be much more effective and provide immediate subjective symptomatic improvements and are, therefore, the preferred modalities of treatment in the control of benign prostate hypertrophy. α_1-Adrenoceptors are also present in blood vessels

and play an important role in the regulation of blood pressure. Thus, α_1-adrenoceptor antagonists are of particular importance as they were originally developed as antihypertensive agents and are likely also to have a beneficial affect on lipid dysfunction and insulin resistance, which are commonly associated with essential hypertension.

The use of α_1-AR antagonists in the treatment of BPH is related to their ability to decrease the tone of prostatic smooth muscle, leading to relief of the obstructive symptoms. Adrenergic receptors found throughout the body play a dominant role in the control of blood pressure, nasal congestion, prostate function and other processes (Harrison *et al.*, Trends Pharmacol. Sci., 1991; 12:62). There are a number of cloned α_1-AR receptor subtypes: α_{1A}-AR, α_{1B}-AR and α_{1D}-AR (Bruno *et al.*, Biochem. Biophys. Res. Commun., 1991; 179:1485; Forray *et al.*, Mol. Pharmacol., 1994; 45:703; Hirasawa *et al.*, Biochem. Biophys. Res. Commun., 1993; 195:902; Ramarao *et al.*, J.Biol. Chem., 1992; 267:21936; Schwinn *et al.*, JPET, 1995; 272:134; Weinberg *et al.*, Biochem. Biophys. Res. Commun., 1994; 201:1296). A number of laboratories have characterized the α_1-ARS in human prostate by function, radioligand binding, and molecular biological techniques (Forray et al., Mol. Pharmacol. 1994; 45:703; Hatano *et al.*, Br.J.Pharmacol, 1994; 113:723; Marshall *et al.*, Br. J.Pharmacol. 1992; 112:59; Marshall *et al.*, Br. J.Pharmacol., 1995; 115:781; Yamada *et al.*,Life Sci., 1994; 54:1845). These studies provide evidence in support of the concept that the α_{1A}-AR subtype comprises the majority of α_1-ARS in human prostatic smooth muscle and mediates contraction in this tissue. These findings suggest that the development of a subtype-selective α_{1A}-AR antagonists might result in a therapeutically effective agent with reduced side effects for the treatment of BPH.

A variety of α_1-AR blockers (terazosin, prazosin, and doxazosin) have been investigated for the treatment of symptomatic bladder outlet obstruction due to BPH, with terazosin (Hytrin, Abbott) being the most extensively studied. Although the α_1-AR blockers are well tolerated, approximately 10-15% of patients develop a clinically adverse event .The undesirable effects of all members of this class are similar, with postural hypotension being the most commonly experienced side effect.

The α_1-AR blocking agents have a more rapid onset of action. However, their therapeutic effect, as measured by improvement in the symptom score and the peak urinary flow rate, is moderate. (Oesterling, N.Engl. J.Med., 1995; 332:99). The vascular side effects (e.g., postural hypertension, dizziness, headaches, etc.) associated with these drugs is due to lack of selectivity of action between prostatic and vascular α_1-adrenoceptors. Clearly, α_1-adrenoceptor antagonists which have inherently greater selectivity for prostatic α_1-adrenoceptors offer the potential of increased urodynamic benefits. This underscores the importance of the discovery of prostate-selective α_1-adrenoceptor antagonists which will confer urodynamic improvement without the side effects associated with existing drugs.

There are many description in the literature about the pharmacological activities associated with α, ω-dicarboximide derivatives. Eur. J .Med . Chem. Chemica Therapeutica; 1977; 12(2):173, J.Indian.Chem.Soc. ,1978; LV:819; J . Indian Chem.Soc., 1979; LVI:1002 discuss the synthesis of these derivatives with CNS and antihypertensive activity . Other references like U.S. Patent Nos. 4,524,206; 4,598,078; 4,567,180; 4,479,954; 5,183,819; 4,748,240; 4,892,943; 4,797,488; 4,804,751; 4,824,999; 4,957,913; 5,420,278; 5,330,762; 4,543,355 and PCT application Nos. WO 98/37893; WO 93/21179, also describe CNS and antihypertensive activity of these compounds. There is no mention of adrenoceptor blocking activity of these compounds and thus their usefulness in the treatment of BPH did not arise.

J.Med.Chem., 1983; 26:203 reports dopamine and α_1-adrenergic activity of some Buspirone analogues. EP 078800 discusses α_1-adrenergic receptor antagonistic activity of pyrimidinedione, pyrimidinetrione and triazinedione derivatives. These compounds, however, had low α_1-adrenergic blocking activity as compared to known α_1-antagonists.

The earlier synthesis of various 1-(4-arylpiperazin-1-yl)-3-(2-oxo-pyrrolidin-1-yl/piperidin-1-yl)alkanes and their usefulness as hypotensive and antischemic agents is disclosed in Indian Patent applications 496/DEL/95, 500/DEL/95 . and 96/DEL/96. These compounds had low α_1-adrenergic blocking activity (pKi ~ 6 as

compared to > 8 of the known α_1-antagonists such as prazosin), and practically no adrenoceptor sub-class selectivity for α_{1A} vs. α_{1B} or α_{1D} adrenoceptors. Further work showed that structural modification of these compounds from lactam to dioxo compounds, i.e., from 2-oxopyrrolidin to 2,5-dioxopyrrolidin and 2,6-dioxopiperidine, enhances the adrenoceptor blocking activity, and also greatly increases the selectivity for α_{1A} in comparison to α_{1B} – adrenoceptor blocking activity, an essential requirement for compounds to be good candidates for treatment of benign prostatic hyperplasia(BPH) disclosed in our U.S. Patent Nos. 6,083,950 and 6,090,809 which are incorporated herein by reference.

OBJECTS OF THE INVENTION

Recently, it has been demonstrated that the prostate tissue of higher species like man and dog has a predominant concentration of α_{1A}-adrenoceptor subtype. This makes it possible to develop agents with selective action against these pathological urodynamic states. The present invention is directed to the development of novel α_1-adrenoceptors and which would thus offer a viable selective relief for prostate hypertrophy as well as essential hypertension, without the side effects associated with known α_{1A}-AR antagonists.

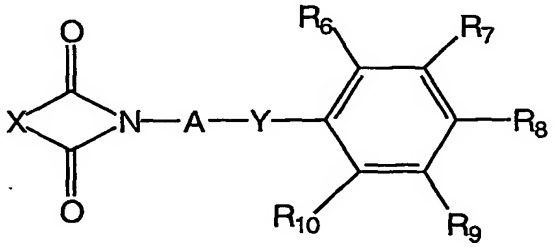
The objective of the present invention therefore is to provide novel α,ω-dicarboximide derivatives that exhibit significantly greater α_{1A}-adrenergic blocking potency than available with known compounds in order to provide specific treatment for benign prostatic hyperplasia.

It is also an object of the invention to provide a process for synthesis of the novel compounds.

It is a further object of the invention to provide compositions containing the novel compounds which are useful in the treatment of benign prostatic hyperplasia.

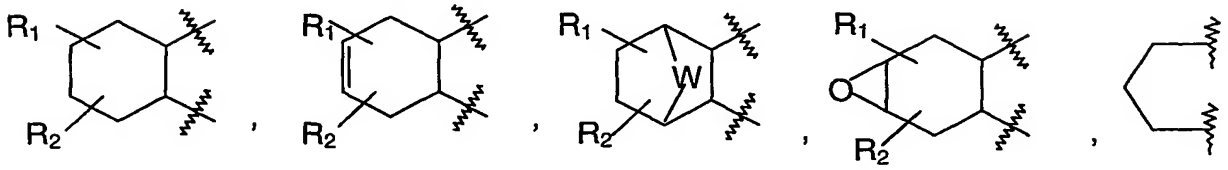
SUMMARY OF THE INVENTION

In order to achieve the above mentioned objectives and in accordance with the purpose of the invention as embodied and described herein, there are provided novel α, ω-dicarboximide derivatives represented by Formula I below;



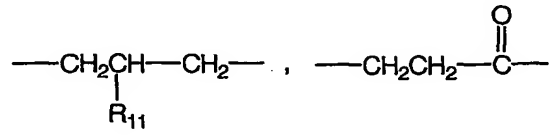
Formula - I

wherein X is selected from the group consisting of



where the points of attachment are depicted by hashed bonds, and where one point of attachment is bonded to the carbonyl adjacent to the nitrogen and the second point of attachment is bonded to the other carbonyl;

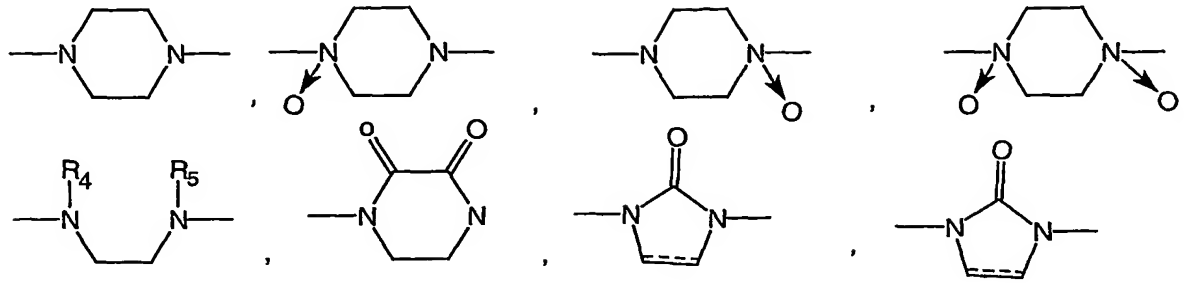
W is O, S, SO or SO_2;

A is $-(CH_2)m-$, 

where m is one of the integers 2,3 or 4;

R_{11} is independently selected from H, F, Cl, Br, I, OH, straight or branched lower (C_{1-6}) alkyl, lower (C_{1-6}) alkoxy, lower (C_{1-6}) perhaloalkyl, lower (C_{1-6}) perhaloalkoxy;

Y is selected from the group consisting of



R_1 and R_2 are independently selected from H, OH, CN, NO_2, Cl, F, Br, I, OR_3, COR_3, $OCOR_3$, $COOR_3$, NH_2, $N(R_4, R_5)$, lower (C_{1-4}) alkyl, lower (C_{1-4}) alkoxy, lower (C_{1-4}) alkylthio, lower (C_{1-4}) perhaloalkyl, lower (C_{1-4}) perhaloalkoxy lower (C_{1-4}) alkoxy substituted with one or more of F, Cl, Br, I, OH, or OR_3, or optionally substituted groups selected from aryl, aralalkyl, heterocyclyl or heteroaryl, said substituents being H, F, Cl, Br, I, OH, OR_3, lower (C_{1-4}) alkyl, lower (C_{1-4}) alkyl substitued with one or more of F, Cl, Br, I, OH or OR_3, wherein R_3, is selected from the group consisting of H, straight or branched C_1-C_6 alkyl or perhaloalkyl; R_4 and R_5 are independently selected from the group consisting of H, CHO, substituted or unsubstituted lower (C_{1-4}) alkyl, lower (C_{1-4}) alkoxy, COR_3, $COOR_3$, $CH_2CH(OR_3)_2$, CH_2COOR_3, CH_2CHO or $(CH_2)_2OR_3$ where R_3 is the same as defined above; R_6, R_7, R_8, R_9 and R_{10} are independently selected from H, OH, CN, NO_2, Cl, F, Br, I, straight or branched lower (C_{1-4}) alkyl, optionally substituted with one or more halogens, lower (C_{1-4}) alkoxy optionally substituted with one or more halogens, (C_{3-6}) cycloalkoxy, NH_2, N-lower (C_{1-4}) alkylamino, N, N-di-lower (C_1-C_4) alkylamino, N-lower (C_1-C_4) alkyl amino carbonyl, hydroxy substituted with aromatic or non-aromatic five or six membered ring, phenyl or phenyl substituted by Cl, F, Br, I, NO_2, NH_2, (C_{1-4}) alkyl or (C_{1-4}) alkoxy, (C_{1-4}) perhaloalkyl, (C_{1-4}) perhaloalkoxy wherein the broken line (----) is a single bond or no bond.

The present invention also provides pharmaceutical compositions for the treatment of benign prostatic hyperplasia. These compositions comprise an effective amount of at least one of the above compounds of Formula I and/or an effective amount of at least one physiologically acceptable acid addition salt thereof, with a pharmaceutically acceptable carrier.

An illustrative list of particular compounds of the invention is given below:

1-[4-(2-Hydroxyphenyl) piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl) propane hydrochloride; (Compound No. 1)

2-[3-{4-(2-(2,2,2-Trifluoroethoxy) phenyl) piperazin-1-yl}propyl]-3a, 4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione hydrochloride; (Compound No. 2)

1-[4-{2-(2,2,2-Trifluoroethoxy)phenyl piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propanehydrochloride; (Compound No. 3)

2-[3-{4-(2-Ethoxyphenyl)piperazin-1-yl, 1-N-oxide} propyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione; (Compound No. 4)

1-[4-(2-Ethoxyphenyl)piperazin-1-yl]-3-(2,6-dioxopiperadin-1-yl)ethane hydrochloride; (Compound No. 5)

2-[3-{4-(2-Methoxyphenyl)piperazin-1-yl}-2-hydroxypropyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione hydrochloride; (Compound No. 6)

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}-2-hydroxypropyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 7)

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl, 1-N-oxide}propyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione; (Compound No. 8)

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl,1,4-N,N-dioxide}propyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3-(2H)-dione; (Compound No. 9)

2-[3-{4-(2-Ethoxyphenyl)piperazin-1-yl,1,4-N,N-dioxide}propyl]-3a-4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione; (Compound No. 10)

2-[3-{4-(2-Ethoxyphenyl)piperazin-1-yl}-2-hydroxypropyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3-(2H)-dione hydrochloride; (Compound No. 11)

2-[3-{4-(2-Ethoxyphenyl)piperazin-1-yl}propyl]-5,6-dihydroxy-3a,4,5,6,7,7a-hexahydro-1H-isoindole-1,3(2H)-dione; (Compound No. 12)

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}propyl]-5,6-dihydoxy-3a,4,5,6,7,7a-hexahydro-1H-isoindole-1,3 (2H)-dione; (Compound No. 13)

2-[3-{4-(2-Hydroxyphenyl)piperazin-1-yl}-2-hydroxypropyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 14)

2-[2-{4-(2-Ethoxyphenyl)piperazin-1-yl}ethyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 15)

2-[2-{4-(2-(2,2,2-Trifluoroethoxy)phenyl)piperazin-1-yl}ethyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione hydrochloride; (Compound No. 16)

2-[3-{4-(2-Ethoxyphenyl)piperazin-1-yl}propyl]-5-chloro-6-hydroxy-3a,4,5,6,7,7a-hexahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 17)

2-[3-{4-(2-Ethoxyphenyl)piperazin-1-yl}propyl]-5-hydroxy-3a,4,5,6,7,7a-hexahydro-1H-isoindole-1,3 (2H)-dione hydrochloride; (Compound No. 18)

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}propyl]-5,6-epoxy-3a,4,5,6,7,7a-hexahydro-1H-isoindole-1,3(2H)-dione; (Compound No. 19)

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}propyl]-5-hydroxy-3a,4,5,6,7,7a-hexahydro-1H-isoindole-1,3(2H)-dione; (Compound No. 20)

2-[3-{4-(2-Isopropoxy-5-hydroxyphenyl)piperazin-1-yl}propyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione hydrochloride; (Compound No. 21)

2-[3-{4-(2-Hydroxyphenyl)piperazin-1-yl, 1-N-oxide}propyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione; (Compound No. 22)

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}propyl]-5,6-dihydroxy-3a,4,5,6,7,7a, hexahydro-1H-isoindole-1,3 (2H)-dione-hydrochloride; (Compound No. 23)

2-[3-{4-(2-Ethoxy-5-hydroxyphenyl)piperazin-1-yl}propyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3-(2H)-dione hydrochloride; (Compound No. 24)

2-[3-{4-(2-Isopropoxy-4-nitrophenyl)piperazin-1-yl}propyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 25)

2-[3-{4-(2-Isopropoxy-4-aminophenyl)piperazin-1-yl}propyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 26)

2-[3-{4-(2-isopropoxy-6-hydroxyphenyl)piperazin-1-yl}propyl]-3a-,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 27)

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}propyl]-5-chloro-6-hydroxy-3a,4,5,6,7,7a-hexahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 28)

1-[4-(2-Isopropoxyphenyl)piperazin-1-yl]-2-hydroxy-3-(2,6-dioxopiperidin-1-yl)propane hydrochloride; (Compound No. 29)

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}-2-hydroxypropyl]-5,6-epoxy-3a,4,5,6,7,7a-hexahydro-1H-isoindole-1,3(2H)-dione; (Compound No. 30)

2-[3-{4-(2-(2,2,2-Trifluoroethoxyphenyl)piperazin-1-yl}-2-hydroxypropyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 31)

2-[3-{4-(2-(2,2,2-Trifluoroethoxy)phenyl)piperazin-1-yl}propyl]-5,6-epoxy-3a,4,5,6,7,7a-hexahydro-1H-isoindole-1,3(2H)-dione; (Compound No. 32)

2-[3-{4-(2-(2,2,2-Trifluoroethoxy)phenyl)piperazin-1-yl}propyl]-5-hydroxy-3a,4,5,6,7,7a-hexahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 33)

2-[3-{4-(2-(2,2,2-Trifluoroethoxy)phenyl)piperazin-1-yl}-2-hydroxypropyl]-5,6-epoxy-3a,4,5,7,7a-hexahydro-1H-isoindole-1,3(2H)-dione; (Compound No. 34)

2-[3-{4-(2-Isopropoxy-3-hydroxyphenyl)piperazin-1-yl}propyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 35)

1-[4-(2-Isopropoxy-5-hydroxyphenyl)piperazin-1-yl]-3-(2,6-dioxopiperdin-1-yl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane hydrochloride; (Compound No. 36)

1-[4-(2-Isopropoxy-6-hydroxyphenyl)piperazin-1-yl]-3-(2,6-dioxopiperdin-1-yl)propane hydrochloride; (Compound No. 37)

1-[4-(2-Isopropoxy-3-hydroxyphenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane hydrochloride; (Compound No. 38)

1-[4-{2-(2,2,2-Trifluoroethoxy)phenyl) piperazin-1-yl]-2-hydroxy-3-(2,6-dioxopiperidin-1-yl)propane hydrochloride; (Compound No. 39)

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}propyl]-4-acetoxy-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 40)

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}propyl]-4-hydroxy-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 41)

2-[N-{N'-(2-Isopropoxyphenyl)aminoethyl}aminopropyl] -3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 42)

2-[3-{4-(2-Cyclopentyloxyphenyl)piperazin-1-yl}propyl]- 3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 43)

1-[4-(2- hydroxyphenyl)piperazin-1-yl]- 2-hydroxy -3-(2,6-dioxopiperidin-1-yl]propane hydrochloride; (Compound No. 44)

2-[3-{4-(2-Biphenyl)piperazin -1-yl}propyl]- 3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 45)

2-[N-{N'-(2-Isopropoxyphenyl) aminoethyl}acetylaminopropyl]- 3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 46)

2-[N-{N'-(2-Isopropoxyphenyl) acetylaminoethyl}aminopropyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 47)

2-[N-[{N'-(2-Isopropoxyphenyl) aminoethyl}hydroxyethyl]aminopropyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 48)

1-[4-(2-Isopropoxyphenyl)piperazin-1-yl]-1-oxo-3-(2,6-dioxopiperidin-1-yl)propane hydrochloride; (Compound No. 49)

2-[N-{N'-(2-Isopropoxyphenyl) aminoethyl}acetaldehyde-aminopropyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione; (Compound No. 50)

2-[N-{N'-(2-Isopropoxyphenyl)aminoethyl} aminopropyl-N,N'-(bis hydroxyethyl]- 3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione; (Compound No. 51)

2-[N-{N'-(2-Isopropoxyphenyl) aminoethyl}ethylacetate-aminopropyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione; (Compound No. 52)

2-[N-{N'-(2-Isopropoxyphenyl) aminoethyl}formylaminopropyl]- 3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione; (Compound No. 53)

2-[3-{4-(2-Isopropoxyphenyl)piperazin-3-oxo-1-yl}propyl]- 3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione; (Compound No. 54)

1-[4-(2- Methoxyphenyl)piperazin-1-yl-4-N-oxide]- 3-(2,6-dioxopiperidin-1-yl]propane; (Compound No. 55)

1-[N-{N'-(2-Methoxyphenyl)aminoethyl}]-3-(2,6-dioxopiperidin-1-yl)aminopropane hydrochloride; (Compound No. 56)

1-[N-N-{N'-(2-Methoxyphenyl)aminoethyl}]-3-(2,6-dioxopiperidin-1-yl)aminopropane hydrochloride; (Compound No. 57)

2-[3-{4-(2-Isopropoxy-4-acetylaminophenyl)piperazin-1-yl}propyl]- 3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 58)

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}propyl]- 7,7a-dihydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 59)

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}-propyl]-4-hydroxy-3a,4,5,6,7,7a-hexahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 60)

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}-propyl]-exo-4,7-epoxy- 3a,4, 7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 61)

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}-1-oxo-propyl]-3a,4, 7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 62)

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}-1-oxo-propyl]-3a,4,5,6, 7,7a-hexahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 63)

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl,4-N-oxide}propyl]-3a,4, 7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione; (Compound No. 64)

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl,1-N-oxide}2-hydroxypropyl]-3a,4, 7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione; (Compound No. 65)

2-[3-{4-(2-Ethoxyphenyl)piperazin-1-yl }propyl]-5,6-dihydroxy-3a,4, 7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 66)

2-[3-{3-(2-Isopropoxyphenyl)imidazolidon-1-yl }propyl]-3a,4, 7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione; (Compound No. 67)

2-[N-{N'-(2-Isopropoxyphenyl)aminoethyl} aminopropyl- N'-(β-hydroxyethyl]- 3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 68)

1-[4-(2- Methoxyphenyl)piperazin-1-yl-1-N-oxide]- 3-(2,6-dioxopiperidin-1-yl]-2-hydroxypropane; (Compound No. 69)

1-[4-(2- Hydroxyphenyl)piperazin-1-yl-1-N-oxide]- 3-(2,6-dioxopiperidin-1-yl]propane; (Compound No. 70)

2-[3-{4-(2-Isopropoxyphenyl)-2,3-dioxopiperazin-1-yl}-propyl]-3a,4, 7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione; (Compound No. 71)

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}propyl]-4,7-dihydroxy-3a,4, 7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione; (Compound No. 72)

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}propyl]-4,7-diacetoxy-3a,4, 7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 73)

2-[N-{N'-(2-Isopropoxyphenyl) aminoethyl}ethylaminopropyl]- 3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione; (Compound No. 74)

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}propyl]-5,6-dimethoxy-3a,4, 7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 75)

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}propyl]-5,6-dimethoxy-3a,4,5,6, 7,7a-hexahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 76)

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}propyl]-4,7-diphenyl-3a,4, 7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 77)

2-[3-{4-(2-Methoxyphenyl)piperazin-1-yl}propyl]-4,7-diphenyl-3a,4, 7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; (Compound No. 78)

Pharmaceutically acceptable, non-toxic, acid addition salts of the compounds of the present invention having the utility of the free bases of Formula I may be formed with inorganic or organic acids, by methods well known in the art and may be used in place of the free bases. Representative examples of suitable acids for

formation of such acid addition salts are maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylene salicylic, methanesulfonic, ethane disulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfamic, phosphoric, hydrobromic, sulfuric, cyclohexylsulfamic, hydrochloric, and nitric acids.

The present invention also includes within its scope prodrugs of the compounds of Formula I. In general, such prodrugs will be functional derivatives of these compounds which are readily converted *in vivo* into the defined compounds. Conventional procedures for the selection and preparation of suitable prodrugs are known.

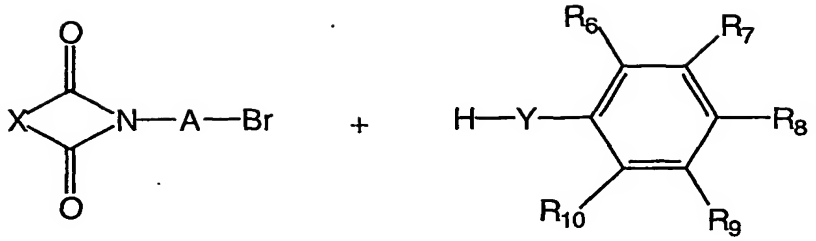
The invention also includes the enantiomers, diastereomers, N-oxides, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates of these compounds, as well as metabolites having the same type of activity. The invention further includes pharmaceutical compositions comprising the molecules of Formula I, or prodrugs, metabolites, enantiomers, diastereomers, N-oxides, polymorphs, solvates or pharmaceutically acceptable salts thereof, in combination with a pharmaceutically acceptable carrier and optionally included excipients.

In yet another aspect, the invention is directed to methods for selectively blocking α_{1A} receptors by delivering in the environment of said receptors, e.g., to the extracellular medium (or by administering to a mammal possessing said receptors), an effective amount of the compounds of the invention.

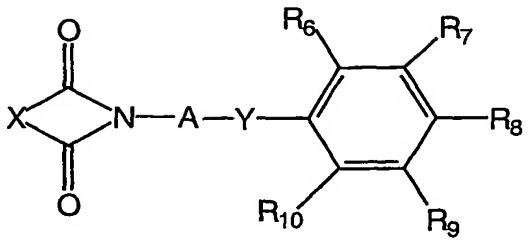
DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention may be prepared by one of the reaction sequences (Schemes I-X) to yield the compounds of Formula I. The starting materials for schemes I-X may be suitably adapted to produce the more specific compounds of Formula I.

SCHEME I

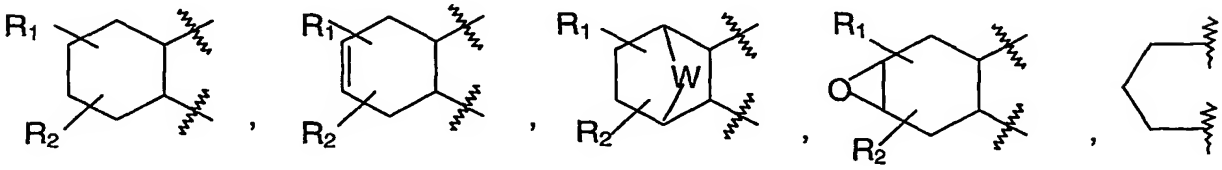


Formula - II **Formula - III**



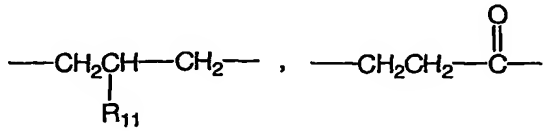
Formula - I

Scheme I shows the synthesis of the compounds of Formula I wherein X is selected from the group consisting of



where the points of attachment are depicted by hashed bonds, and where one point of attachment is bonded to the carbonyl adjacent to the nitrogen and the second point of attachment is bonded to the other carbonyl;

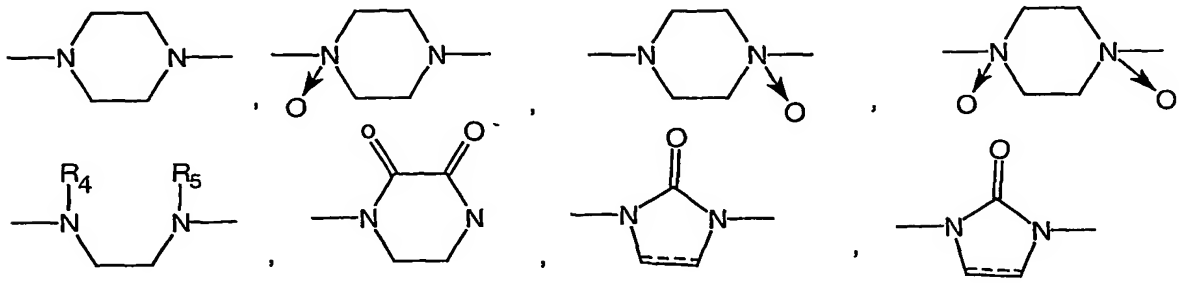
W is O, S, SO or SO_2;

A is $-(CH_2)m-$, 

where m is one of the integers 2,3 or 4;

R_{11} is independently selected from H, F, Cl, Br, I, OH, straight or branched lower (C_{1-6}) alkyl, lower (C_{1-6}) alkoxy, lower (C_{1-6}) perhaloalkyl, lower (C_{1-6}) perhaloalkoxy;

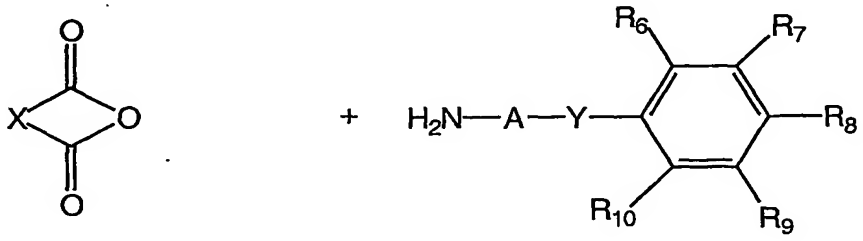
Y is selected from the group consisting of



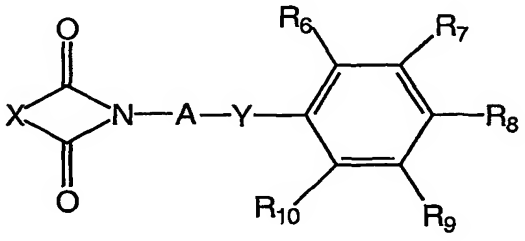
R_1 and R_2 are independently selected from H, OH, CN, NO_2, Cl, F, Br, I, OR_3, COR_3, $OCOR_3$, $COOR_3$, NH_2, N(R_4, R_5), lower (C_{1-4}) alkyl, lower (C_{1-4}) alkoxy, lower (C_{1-4}) alkylthio, lower (C_{1-4}) perhaloalkyl, lower (C_{1-4}) perhaloalkoxy lower (C_{1-4}) alkoxy substituted with one or more of F, Cl, Br, I, OH, or OR_3, or optionally substituted groups selected from aryl, aralalkyl, heterocyclyl or heteroaryl, said substituents being H, F, Cl, Br, I, OH, OR_3, lower (C_{1-4}) alkyl, lower (C_{1-4}) alkyl substitued with one or more of F, Cl, Br, I, OH or OR_3, wherein R_3, is selected from the group consisting of H, straight or branched C_1-C_6 alkyl or perhaloalkyl; R_4 and R_5 are independently selected from the group consisting of H, CHO, substituted or unsubstituted lower (C_{1-4}) alkyl, lower (C_{1-4}) alkoxy, COR_3, $COOR_3$, $CH_2CH(OR_3)_2$, CH_2COOR_3, CH_2CHO or $(CH_2)_2OR_3$ where R_3 is the same as defined above; R_6, R_7, R_8, R_9 and R_{10} are independently selected from H, OH, CN, NO_2, Cl, F, Br, I, straight or branched lower (C_{1-4}) alkyl, optionally substituted with one or more halogens, lower (C_{1-4}) alkoxy optionally substituted with one or more halogens, (C_{3-6}) cycloalkoxy, NH_2, N-lower (C_{1-4}) alkylamino, N, N-di-lower (C_1-C_4) alkylamino, N-lower (C_1-C_4) alkyl amino carbonyl, hydroxy substituted with aromatic or non-aromatic five or six membered ring, phenyl or phenyl substituted by Cl, F, Br, I, NO_2, NH_2, (C_{1-4}) alkyl or (C_{1-4}) alkoxy, (C_{1-4}) perhaloalkyl, (C_{1-4}) perhaloalkoxy wherein the broken line (----) is a single bond or no bond.

The preparation comprises condensing α,ω-dicarboximides of Formula II with substituted phenyl of Formula III, in the presence of a base and an organic solvent at a temperature ranging from about 70-150° C for a period varying between 8-24 hours to produce the corresponding compounds of Formula I. The suitable organic solvent is a dipolar aprotic solvent selected from the group consisting of dimethylsulfoxide, N, N-dimethylformamide, hexamethylphosphoramide and N-methyl-2-pyrrolidone. The reaction is carried out in the presence of an inorganic base preferably selected from the group potassium carbonate and sodium carbonate. The preferable temperature conditions for the reaction are 70-80° C.

SCHEME II



Formula - V **Formula - IV**

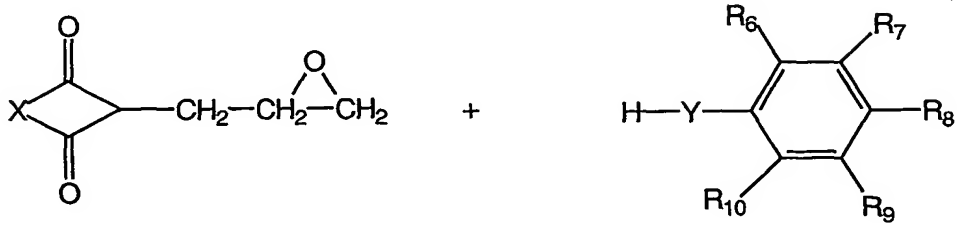


Formula - I

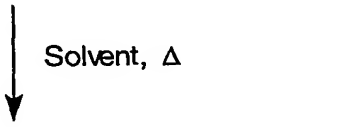
The compounds of the Formula I can also be prepared by Scheme II, wherein substituted phenyl of the Formula IV is condensed with the anhydrides of Formula V, to give compounds of Formula I, wherein X, Y, A, R_6, R_7, R_8, R_9 and R_{10} as defined above. The reaction is carried out under reflux conditions in an organic solvent such

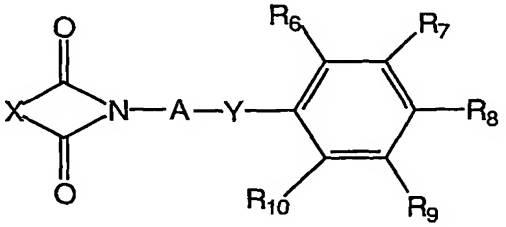
as toluene, benzene, xylene, pyridine, acetic acid in pyridine, or mixtures thereof. The preferable temperature condition for the reaction is 70-80° C.

SCHEME III



Formula - VI **Formula - III**



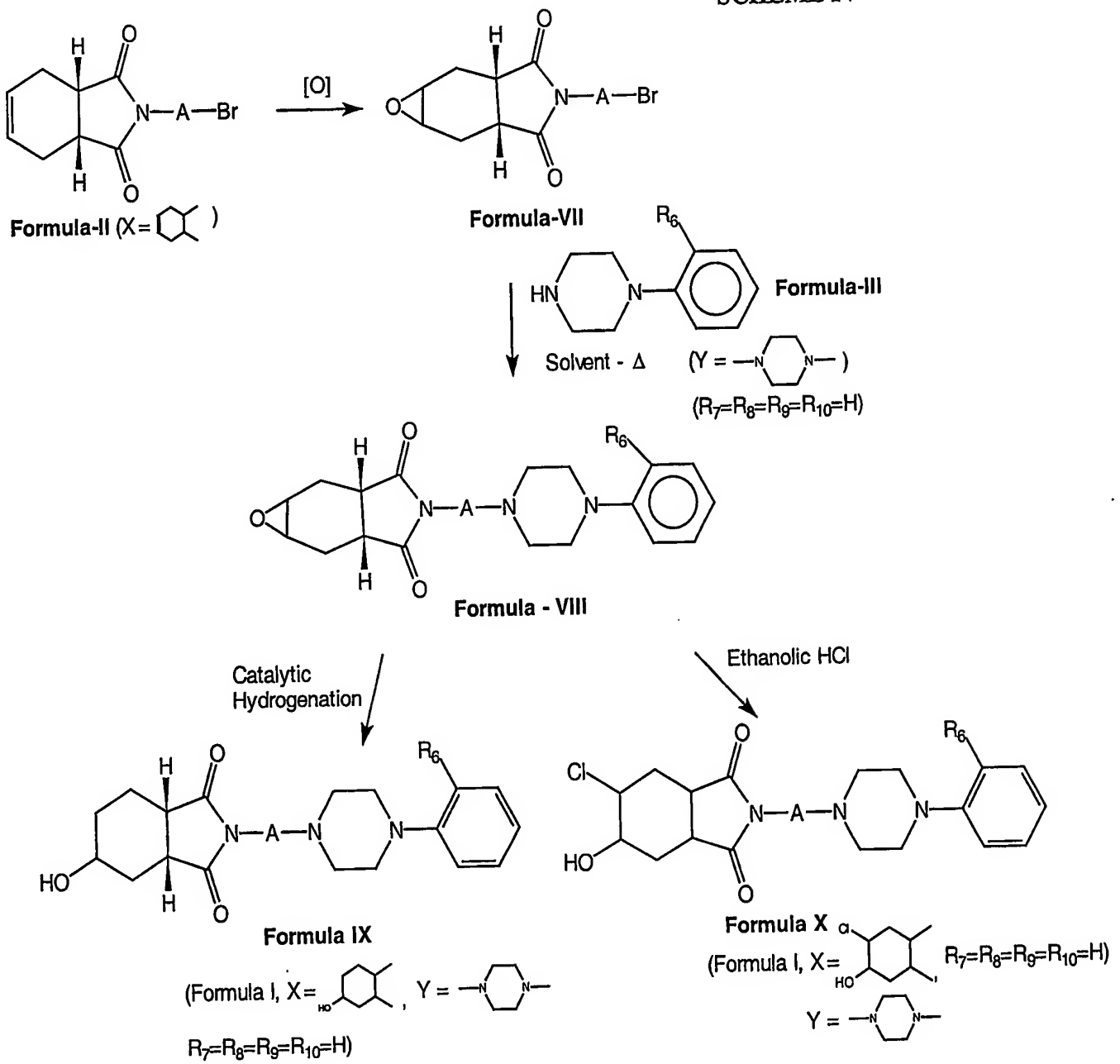


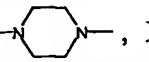
Formula - I (A = CH_2—CH(OH)—CH_2—)

Scheme III shows the synthesis of the compounds of Formula I (when A = -CH_2-CH- CH_2) which comprises the nucleophilic ring opening of the epoxide of Formula VI with the substituted phenyl of the Formula III, wherein X, Y, R_6, R_7, R_8, R_9 and R_{10} are as defined earlier and A is -CH_2- CH(OH)- CH_2-. Preferably, the reaction is carried out in organic solvent at a temperature ranging from 50-100° C for a period ranging from one to several hours. The solvent for carrying out this reaction is a dipolar aprotic solvent such as dimethylsulfoxide, N, N-dimethylformamide, sulfolane, dimethylacetamide, hexamethylphosphamide and N-methyl-2-pyrrolidine. Polar protic solvents like ethanol can also be used under reflux conditions for this reaction. The reaction can be carried out in the presence of inorganic base such as potassium carbonate or sodium carbonate, or an organic base such as triethyl amine

and diisopropylethylamine. The suitable temperature range for the reaction is 70-80°C.

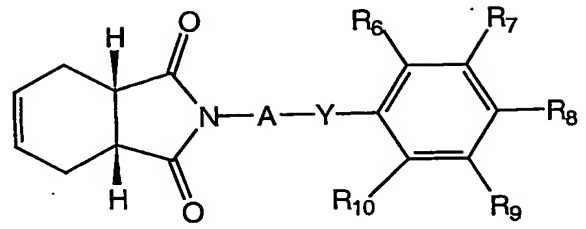
SCHEME IV


[O]
Formula-II (X=
Formula-VII
Formula-III
Solvent - Δ
(Y =
(R7=R8=R9=R10=H)
Formula - VIII
Catalytic Hydrogenation
Ethanolic HCl
Formula IX
(Formula I, X=
Y =
R7=R8=R9=R10=H)
Formula X
(Formula I, X=
R7=R8=R9=R10=H)
Y =

The compounds of Formula IX (Formula I, when X =  , Y=  , $R7= R_8=R_9=R_{10}=H$) can be prepared by the reaction sequence of Scheme IV, wherein A and R_6 are as defined earlier. The starting material for this scheme is the compound of Formula II (when X = ) which is subjected to epoxidation to give a compound of Formula VII wherein A is same as defined earlier. The reaction of epoxidation is carried out in a nonpolar solvent or a polar aprotic solvent at sub-zero temperatures for a period of 24-30 hours. The product (Formula VII) formed is then condensed with substituted phenyl of Formula III (when Y=  , $R_7 = R_8 = R_9= R_{10}=H$) in the presence of a base and an organic solvent at a temperature ranging from 70-150° C for a period varying between 8-24 hours to produce compound of Formula VIII. Nucleophilic ring opening of epoxide of compound of Formula VIII with alcoholic hydrochloric acid gave corresponding compound of Formula X, while catalytic hydrogenation of compounds of Formula VIII in a polar solvent at reduced pressure, for a period ranging between 36-72 hours gave corresponding compounds of Formula IX.

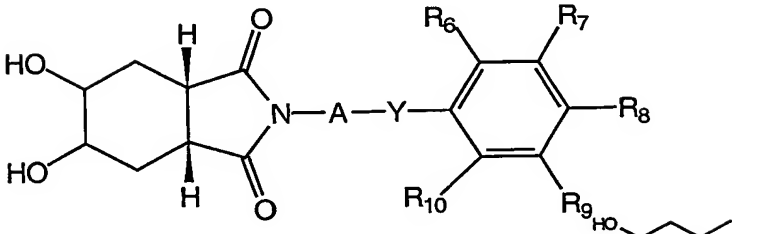
The epoxidation of compounds of Formula II is carried out with peracid such as metachloroperbenzoic acid, peracetic acid or trifluoroperacetic acid. The organic solvent used in this reaction can be selected from a group consisting of dichloromethane, dichloroethane, chloroform, tetrahydrofuran, acetone and acetonitrile. The preferred temperature conditions are 0-5° C. The condensation of the epoxide of Formula VII with compound of Formula III is carried out in a polar aprotic solvent such as dimethylsulfoxide, N,N-dimethylformamide, sulfolane, dimethylacetamide hexamethylphosphoramide and N-methyl-2-pyrrolidone. The inorganic base used in this reaction is selected from the group consisting of potassium carbonate and sodium carbonate and the preferable temperature for carrying out this reaction is 50-55° C. The nucleophilic epoxide ring opening of compounds of Formula VIII is carried out preferably with methanolic or ethanolic hydrochloric acid while the catalytic hydrogenation of the epoxide of compounds of Formula VIII is carried out in polar protic solvents such as methanol and ethanol.

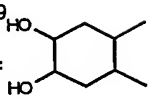
SCHEME V

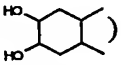


Formula-XI (Formula I, X= )

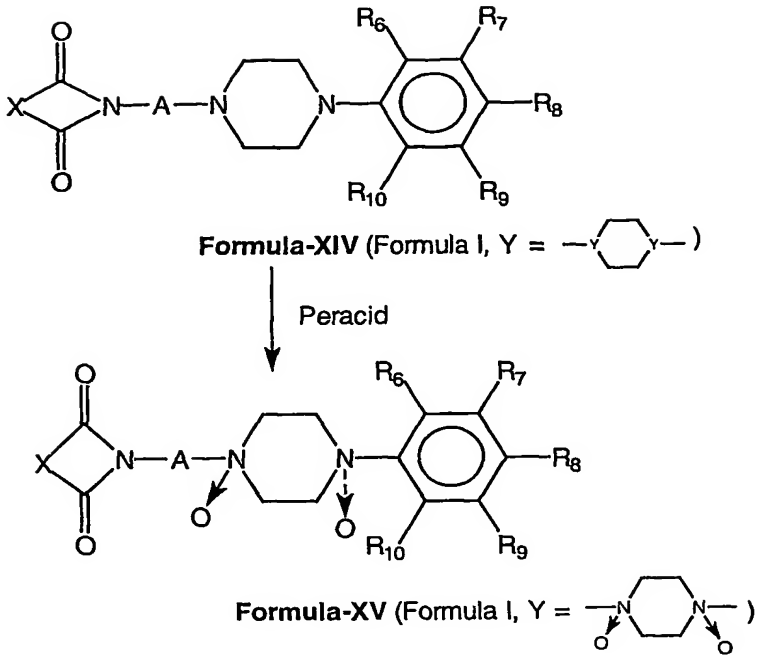
[O]



Formula - XII (Formula I, X= )

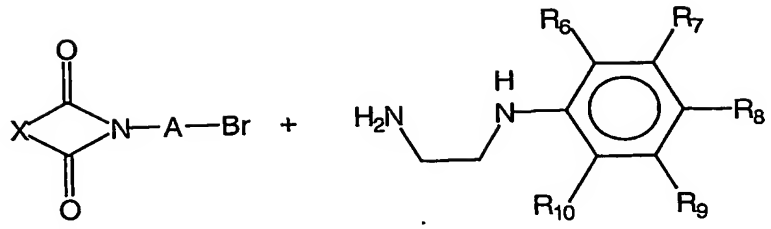
The compounds of Formula XII (Formula I when X = ) is prepared by the method of Scheme V with Y, A, R_6, R_7, R_8, R_9, and R_{10} groups as defined earlier. The starting material for Scheme V is the compound of Formula XI (Formula I, when X = ) which is subjected to oxidation to give the corresponding diol of Formula XII. The reaction is carried out preferably in a polar solvent at about 0-5° C for about one to several hours. The oxidizing agent in this reaction is selected from the group consisting of osmium tetraoxide and potassium permanganate. The reaction is carried out in a polar protic or aprotic solvent such as methanol, ethanol, acetone, and acetonitrile. The preferable temperature range is 0-5° C.

SCHEME VI



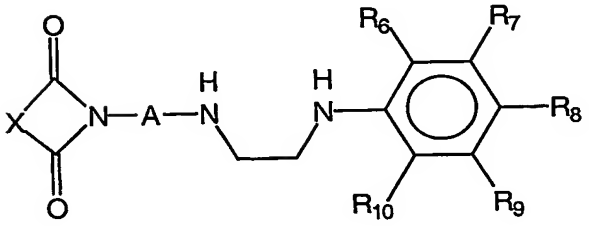
The compounds of Formula XV (Formula I, when Y =) is prepared by following the reaction sequence of Scheme VI with X, A, R_6, R_7, R_8, R_9 and R_{10} groups as defined earlier. The starting materials for Scheme VI are compound of Formula XIV (Formula I, when Y =) which upon treatment with peracid such as metachloroperbenzoic acid in an organic solvent at sub zero temperature for a period varying between 2-8 hours gives the corresponding N-Oxides of Formula XV.

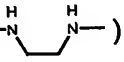
SCHEME VII

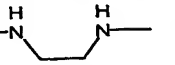


Formula-II **Formula XVI**

DMF/Base

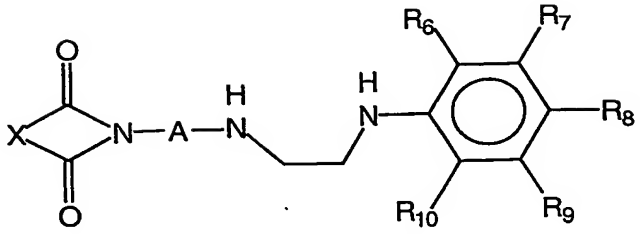


Formula-XVII (Formula I, Y = )

Scheme VII reveals the synthesis of the compounds of Formula XVII (Formula I, when Y = ), wherein X, A, R_6, R_7, R_8, R_9 and R_{10} are as defined earlier. The preparation comprises condensing α,ω-dicarboximides of Formula II with ethylene diamines of Formula XVI in the presence of a base and an organic solvent at a temperature ranging from 70-80° C for a period varying between 8-24 hours to produce the corresponding compounds of Formula XVII.

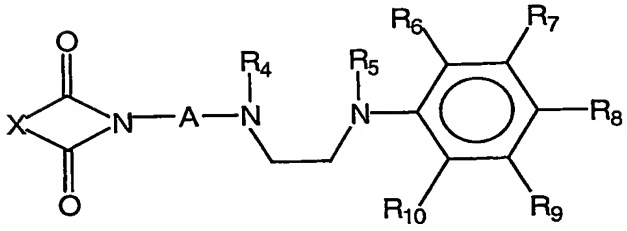
The suitable organic solvent is a dipolar aprotic solvent, which is selected from the group consisting of dimethyl sulfoxide, N, N-dimethylformamide, sulfolane, dimethyl acetamide, hexamethyl phosphoramide and N-methyl-2-pyrrolidone. The reaction is carried out in the presence of an inorganic base, preferably selected from the group consisting of potassium carbonate and sodium carbonate. The preferable temperature conditions for the reaction are 70-80° C.

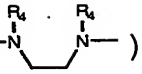
SCHEME VIII

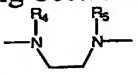


Formula-XVIII

Solvent/Base

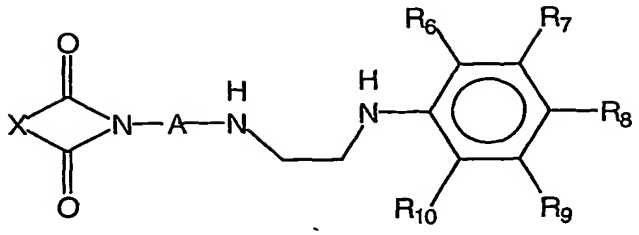


Formula-XIX (Formula I, Y = )

The compounds of Formula XVIII are alkylated in the presence of an inorganic base and organic solvent at a temperature ranging between 20-150° C for a period varying between 5-24 hours to give the compounds of Formula XIX (Formula I, when Y = ) with X, A, R_4, R_5, R_6, R_7, R_8, R_9 and R_{10} are the same as defined earlier.

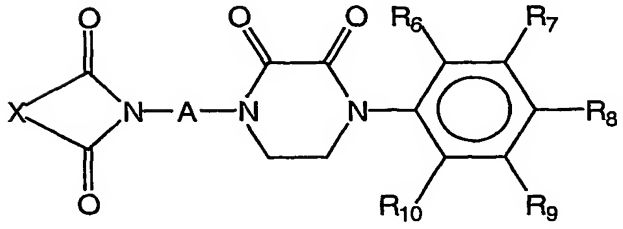
The suitable organic solvent is a dipolar aprotic solvent which is selected from the group consisting of dimethylsulfoxide, N,N-dimethylformamide, sulfolane, dimethylacetamides, hexamethyl phosphoramide and N-methyl-2-pyrrolidone. The reaction is carried out in the presence of an inorganic base, preferably selected from the group consisting of potassium carbonate, sodium carbonate and sodium hydride. The preferable temperature conditions for the reaction are 120-150° C.

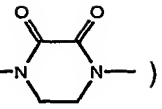
SCHEME IX

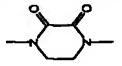


Formula XVIII

Oxalyl Chloride/Base

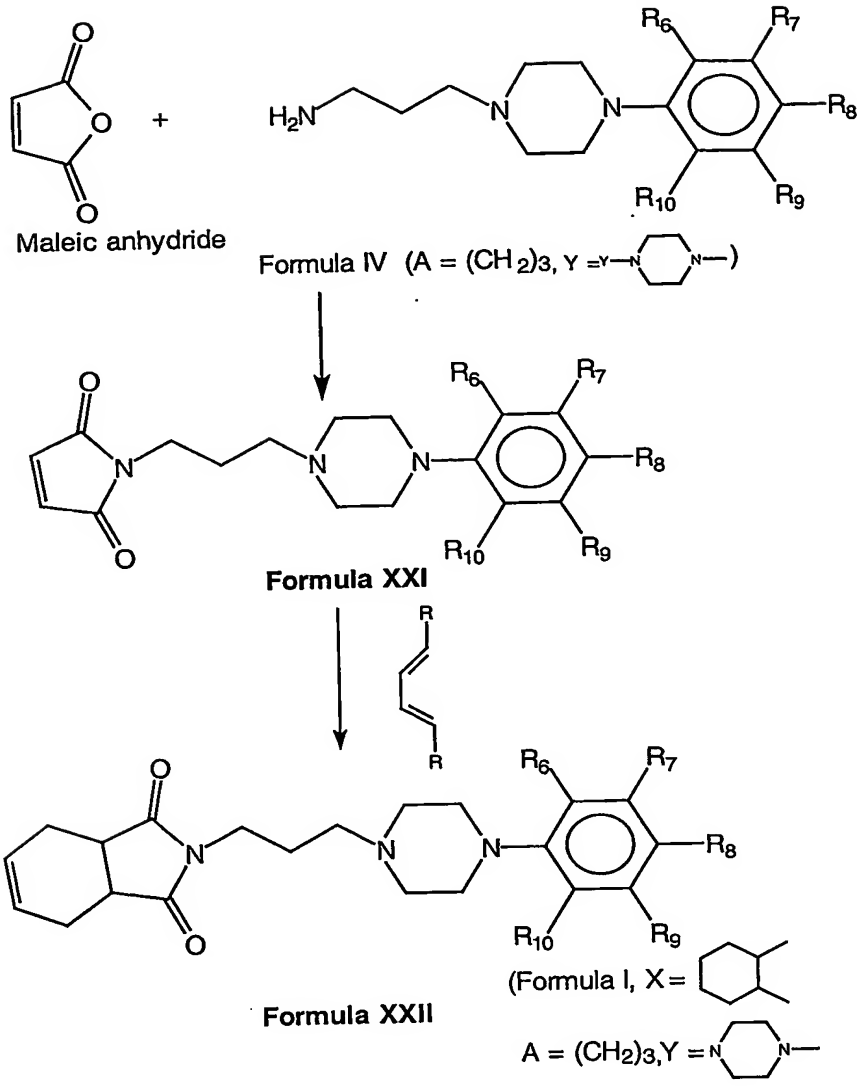


Formula-XX Formula I, Y = 

The compounds of Formula XVIII are treated with oxalyl chloride in the presence of an organic base and organic solvent at temperature ranging between 0-20° C for a period varying between 1-5 hours which yields the corresponding dioxopiperazine of Formula XX (Formula I, when Y=  , with X, A, R_6, R_7, R_8, R_9 and R_{10} are the same as defined earlier.

The suitable organic solvent is selected from the group consisting of dichloromethane, dichloroethane, chloroform and tetrahydrofuran. The reaction is carried out in the presence of an organic base preferably selected from the group triethylamine and diisopropyl ethylamine.

SCHEME X



Scheme X shows the synthesis of the compounds of Formula XXII (Formula I, when x = , A = -$(CH_2)_3$, Y =) in which R_6, R_7, R_8, R_9 and R_{10} are as defined earlier which comprises condensing maleic anhydride with substituted phenyl piperazine of Formula IV(A = $(CH_2)_3$, Y=) in an organic solvent under reflux condition with azeotropic removal of water to give the corresponding α,ω- dicarboxiimide of Formula XXI which is further subjected to Diels Alder addition with substituted butadienes in a non-polar organic solvent under reflux conditions to give the corresponding compounds of Formula XXII. The non-polar organic solvent for carrying out this reaction is chosen from the group consisting of toluene, benzene and xylene. The preferable temperature conditions are 70-80° C.

The examples mentioned below demonstrate the general synthetic procedure as well as the specific preparation of the preferred compounds. The examples are given to illustrate the details of the invention and should not be construed to limit the scope of the present invention.

EXAMPLE 1
(Scheme I)

Preparation of 2-[3-{4-(4-(2-(2,2,2-Trifluoroethoxy)phenyl)piperazin-1-yl} propyl]-3a,4,7,7a-tetrahydro-1-H-isoindole-1,3-(2H)-dione hydrochloride;

A mixture of 1-(3-bromopropyl)-cis-3a,4,7,7a-tetrahydrophthalimide (1g, 3.67 mmol), 1-(2-(2,2,2-trifluoroethoxy)phenyl)piperazine (1.43g, 5.5 mmol) and potassium iodide (0.036 g, 0.22 mmol) in N,N-dimethyl formamide (25 ml) was heated at 70-80° C for about 12 hours. After the reaction was over, solvent was evaporated under reduced pressure, the residue was suspended in water (100 ml) and extracted with ethyl acetate (2x50 ml). The combined ethyl acetate layer was washed with water (2x50 ml), dried over anhydrous sodium sulphate, and the solvent evaporated *in vacuo* to yield crude oil. The product was purified by chromatography on silica gel, using dichloromethane/methanol (98/2, v/v) as eluent to afford the suitable compound 1g as an oil. The compound so obtained was converted in to its hydrochloride salt as off-white solid (m.p. 204-208° C).

MS: m/z 452.3 (MH^+), IR (KBr cm^{-1}): 1697.7 (C=O)
^{1}HNMR (DMSO-d_6) δ: 1.92 (2H, m), 2.23-2.39 (4H, dd), 3.05-3.19 (8H, m), 3.43-3.55 (6H, m), 4.69-4.73 (2H, q), 5.89 (2H, s), 7.03-7.06 (4H, m).

An illustrative list of the compounds of the invention which were synthesised by the above method is given below:

1-[4-(2-Hydroxyphenyl) piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl) propane hydrochloride; mp 224-227 °C.

1-[4-{2-(2,2,2-Trifluoroethoxy)phenyl piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane-hydrochloride; m.p. 208-212° C.

1-[4-(2-Ethoxyphenyl)piperazin-1-yl]-3-(2,6-dioxopiperadin-1-yl)ethane hydrochloride; m.p. 199-202° C.

2-[2-{4-(2-Ethoxyphenyl)piperazin-1-yl}ethyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride, m.p. 220-222° C.

2-[2-{4-(2-(2,2,2-Trifluoroethoxy)phenyl)piperazin-1-yl}ethyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione hydrochloride; m.p. 178-180° C.

2-[3-{4-(2-Isopropoxy-5-hydroxyphenyl)piperazin-1-yl}propyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione hydrochloride; m.p. 238-242° C.

2-[3-{4-(2-Ethoxy-5-hydroxyphenyl)piperazin-1-yl}propyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3-(2H)-dione hydrochloride; m.p. 234-236° C.

2-[3-{4-(2-Isopropoxy-4-nitrophenyl)piperazin-1-yl}propyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; m.p. 199-203 ° C.

2-[3-{4-(2-Isopropoxy-4-aminophenyl)piperazin-1-yl}propyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; m.p. 220-222° C.

2-[3-{4-(2-isopropoxy-6-hydroxyphenyl)piperazin-1-yl}propyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; m.p.217-220° C.

2-[3-{4-(2-isopropoxy-3-hydroxyphenyl)piperazin-1-yl}propyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; m.p. 212-216° C.

1-[4-(2-Isopropoxy-5-hydroxyphenyl)piperazin-1-yl]-3-(2,6-dioxopiperdin-1-yl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane hydrochloride; m.p. 218-222° C.

1-[4-(2-Isopropoxy-6-hydroxyphenyl)piperazin-1-yl]-3-(2,6-dioxopiperdin-1-yl)propane hydrochloride; m.p. 215-219° C.

1-[4-(2-Isopropoxy-3-hydroxyphenyl)piperazin-1-yl]-3-(2,6-dioxopiperidin-1-yl)propane hydrochloride; m.p. 260-263° C.

2-[3-{4-(2-Cyclopentyloxyphenyl)piperazin-1-yl}propyl]- 3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; mp 185-189 ° C.

2-[3-{4-(2-Biphenyl)piperazin -1-yl}propyl]- 3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride ;mp 164-168 ° C.

1-[4-(2-Isopropoxyphenyl)piperazin-1-yl]-1-oxo-3-(2,6-dioxopiperidin-1-yl)propane hydrochloride; m.p. 174-177° C.

2-[3-{4-(2-Isopropoxy-4-acetylaminophenyl)piperazin-1-yl}propyl]- 3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; mp 226-228° C.

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}-1-oxo-propyl]-3a,4, 7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride ;m.p 220-222° C.

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}-1-oxo-propyl]-3a,4,5,6, 7,7a-hexahydro-1H-isoindole-1,3(2H)-dione hydrochloride ;m.p.227-229° C.

EXAMPLE 2
(Scheme III)

Preparation of 2-[3-{4-(2-isopropoxyphenyl)piperazin-1-yl}-2-hydroxypropyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride;

A mixture of 1-(2,3-epoxypropyl)-cis-3a,4,7,7a-tetrahydrophthalimide (0.5 g, 2.42 mmol), 1-(2-isopropoxyphenyl)piperazine (0.48 g, 2.18 mmol) and triethylamine (0.27 g, 2.67 mmol) in ethanol (35 ml) were refluxed for 5 hours. After the reaction was over, the solvent was removed under reduced pressure .The residue thus obtained was suspended in water (50 ml), and extracted with dichloromethane (2x50 ml). The combined dichloromethane layer was washed with water (50 ml), dried over anhydrous sodium sulphate, and finally concentrated to yield a crude oil. The product was purified by chromatography on silica gel, using chloroform/methanol (98/2, v/v) to afford the product 0.8 g (77.7%) as an oil.

The hydrochloride salt was prepared by the addition of equimolar quantity of ethereal hydrochloride to the ethanolic solution of free base. The solid was precipitated by the addition of diethylether and collected by filtration. m.p. 206-209° C.

MS: m/z 429 (MH^+)
IR (KBr cm^{-1}) 3369.3 (-OH), 1695 (C=0)
^{1}HNMR ($CDCl_3$) δ: 1.38-1.40 (6H, d), 2.19-2.26 (2H, dd), 2.57-2.63 (2H, dd), 3.09-3.24 (5H, m), 3.52-3.58 (4H, m), 3.65-3.69 (4H, m), 3.72-3.76 (1H, d), 4.58-4.64 (2H, m), 5.89-5.91 (2H, m), 6.88-6.93 (2H, m), 7.05-7.10 (2H, m).

An illustrative list of the compounds of the invention which were synthesised by the above method is given below:

2-[3-{4-(2-Methoxyphenyl)piperazin-1-yl}-2-hydroxypropyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione hydrochloride; m.p. 205-207° C,

2-[3-{4-(2-Ethoxyphenyl)piperazin-1-yl}-2-hydroxypropyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3-(2H)-dione hydrochloride; m.p. 224-226° C,

2-[3-{4-(2-Hydroxyphenyl)piperazin-1-yl}-2-hydroxypropyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; m.p. 258-260° C,

1-[4-(2-Isopropoxyphenyl)piperazin-1-yl]-2-hydroxy-3-(2,6-dioxopiperidin-1-yl)propane hydrochloride; m.p. 180-183° C,

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}-2-hydroxypropyl]-5,6-epoxy-3a,4,5,6,7,7a-hexahydro-1H-isoindole-1,3(2H)-dione; m.p. obtained as oil.

2-[3-{4-(2-(2,2,2-Trifluoroethoxyphenyl)piperazin-1-yl}-2-hydroxypropyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; m.p. 183-186° C,

2-[3-{4-(2-(2,2,2-Trifluoroethoxy)phenyl)piperazin-1-yl}-2-hydroxypropyl]-5,6-epoxy-3a,4,5,7,7a-hexahydro-1H-isoindole-1,3(2H)-dione; m.p. oil.

1-[4-{2-(2,2,2-Trifluoroethoxy)phenyl)piperazin-1-yl]-2-hydroxy-3-(2,6-dioxopiperidin-1-yl)propane hydrochloride; m.p. 146-150 °C,

1-[4-(2-hydroxyphenyl)piperazin-1-yl]-2-hydroxy-3-(2,6-dioxopiperidin-1-yl]propane hydrochloride; m.p. 202-207 ° C.

EXAMPLE 3
(Scheme II)

Preparation of 2-[3-{4-(2-isopropoxyphenyl) piperazin-1-yl} propyl) piperazin-1-yl} propyl]-4-hydroxy-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride

Example 3A

Preparation of 2-[3-{4-(2-Isopropoxyphenyl) piperazin-1-yl} propyl]-4-acetoxy-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione hydrochloride;

A mixture of 1-amino-3-[4-(2-isopropoxyphenyl) piperazin-1-yl] propane (1.19g, 4.3 mmol) and 3-acetoxy-1,2,3,6-tetrahydrophthalic anhydride (1g, 4.77 mmol) in toluene (10 ml) was refluxed for 3 hours. After the reaction was over, solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (20 ml). The ethyl acetate solution was washed with water (2x10 ml), dried over anhydrous sodium sulphate, and concentrated *in vacuo* to yield crude oil. The product was purified by chromatography on silica gel, using dichloromethane/methanol (98/2, v/v) as eluent to afford 1.2 g product as a yellowish oil Yield: 59.7%. The compound so obtained was onverted in to its hydrochloride salt (m.pt. 224-227° C).

MS: m/z 470 (MH^+)
IR (KBr cm^{-1}) 1699.6 (CO)

^1H NMR ($CDCl_3$) δ : 1.36-1.38 (6H, d), 2.08 (3H, s), 2.22-2.25 (3H, m), 2.66 (1H, m), 3.01-3.02 (4H, m), 3.25-3.27 (1H, m), 3.52-3.65 (9H, m), 4.58-4.60 (1H, m), 5.39-5.42 (1H, m), 6.05-6.06 (2H, m), 6.86-6.92 (3H, m), 7.00-7.03 (1H, m), 12.75 (1H, br s).

Example 3B

Preparation of 2-[3-{4-(2-isopropoxyphenyl) piperazin-1-yl} propyl) piperazin-1-yl} propyl]-4-hydroxy-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride

The product of Example 3A (compound 49) (0.7g, 1.38 mmol) was dissolved in IN methanolic hydrochloride (5 ml) and stirred for 3 hours at room temperature. After the reaction was over, the pH of the reaction mixture was adjusted to 7, using sodium bicarbonate solution (5% w/v), and extracted with dichloromethane (2x20 ml). The combined dichloromethane layer was washed with water (10 ml), dried over anhydrous sodium sulphate, and concentrated *in vacuo* to yield the crude product as an oil. The product thus obtained was purified using dichloromethane/methanol (98/2 v/v) as eluent to afford 0.51 g of the product as oil. Yield: 86.3%. The product thus obtained was converted in to its hydrochloride salt (m.pt. 186-190° C).

MS: m/z 428 (MH^+)

^1H NMR ($CDCl_3$) δ: 1.35-1.37 (6H, d), 2.37-2.47 (3H, m), 2.78-2.84 (1H, d), 3.07-3.12 (6H, m), 3.50-3.59 (6H, m), 3.64-3.68 (2H, m), 4.58-4.63 (2H, m), 5.97-5.60 (1H, m), 6.13-6.14 (1H, m) 6.13-6.14 (1H, m), 6.86-6.95 (3H, m), 7.01-7.04 (1H, m), 12.12 (1H, brs)

An illustrative list of the compounds of the invention which were synthesised by the above method is given below:

2-[3-{4-(2-Isopropoxyphenyl) piperazin-1-yl} propyl]-4,7-dihydroxy-3a,4, 7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride, m.p. 208-210° C,

2-[3-{4-(2-Isopropoxyphenyl) piperazin-1-yl}-propyl]-exo-4,7-epoxy- 3a,4, 7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; m.p. 194-196° C,

2-[3-{4-(2-Isopropoxyphenyl) piperazin-1-yl}-propyl]-4,7-dihydroxy-3a,4, 7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride; m.p. 208-210° C.

EXAMPLE 4
(Scheme IV)

Preparation of 2-[3-{4-(2-isopropoxyphenyl)piperazin-1-yl}propyl]-5-hydroxy-3a,4,5,6,7,7a-hexahydro-1H-isoindole-1,3 (2H)-dione hydrochloride

Example 4A

Preparation of 2-(3-Bromopropyl)-5,6-epoxy-as-3a, 4,5,6,7,7a-hexahydro-1H-isoindole-1,3 (2H)-dione (intermediate)

2-(2-Bromopropyl)-cis-3a, 4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione (ref. 6g, 220 mmol) was dissolved in dichloromethane (50 ml) and cooled to 0° C. A solution of m-chloroperbenzoic acid (3.8g, 220 mmol) in dichloromethane (25 ml) was then added slowly over a period of 15 minutes to the above solution at 0-5° C. The reaction mixture was further stirred for 24 hours at the same temperature. After the reaction was over, the reaction mixture was poured in to a stirred aqueous potassium carbonate solution (2.5%, 200 ml). The resulting mixture was extracted with dichloromethane (2x100 ml). The combined organic layer was dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure and the crude product thus obtained was crystallised with ethyl acetate-hexane to afford 5g (79%) of the required intermediate which was used as such in the next step.

Example 4B

Preparation of 2-[3-{4-isopropoxyphenyl)piperazin-1-yl}propyl]-5,6-epoxy 3a,4,5,6,7,7a-hexahydro-1H-isoindole-1,3(2H)-dione

The intermediate compound resulting from Example 4A (4.93g, 17.1 mmol) was dissolved in dimethylformamide (25 ml). To this solution, 1-(2-isopropoxyphenyl) piperazine hydrochloride (4g, 15.5 mmol) was added followed by anhydrous potassium carbonate (4.29g, 31 mmol). The reaction mixture was heated at 50° C for about 16 hours. After the reaction was over, the solvent was removed under reduced pressure and the residue thus obtained was suspended in cold water (100 ml) and extracted with ethyl acetate (2x100 ml). The combined ethyl acetate layer was washed with water (2x100 ml) and dried over anhydrous sodium sulphate. The organic layer was concentrated *in vacuo* and purified by chromatography on silica gel using 4% methanol in dichloromethane as eluent to yield the title compound as an oil. Yield 6g (90%)

MS m/z : 427.9 (MH^+)
IR (DCM cm^{-1}) : 1698.7 (C=O)
^1H NMR (300 MHz, $CDCl_3$) δ: 1.33 (6H, d), .81-1.86 (2H, m); 2.13-2.20 (2H, m), 2.46 (2H, t), 2.6 (4H, s), 2.70-2.75 (4H, m), 3.09-3.15 (6H, m), 3.59 (2H, t), 4.57-4.61 (1H, m), 6.83-6.92 (4H, m)

Example 4C

Preparation of 2-[3-{4-(2-Isopropoxyphenyl) piperazine-1-yl} propyl]-5-hydroxy-3a,4,5,6,7,7a-hexahydro-1H-isoindole-1,3(2H)-dione hydrochloride

The compound resulting from Example 4B (0.5 g, 1.17 mmol) was dissolved in methanol (25 ml) and 10% Pd/c (0.5g) was added. The reaction mixture was hydrogenated at 70 psi for 36 hours. After the reaction was over, the catalyst was filtered, washed with methanol (10 ml) and the solvent was evaporated. Water (50 ml) was added to the residue and extracted with dichloromethane (2x50 ml). The combined organic layer was washed with water (50 ml), dried over anhydrous sodium sulphate and concentrated. The product was purified by chromatography on silica gel using 5% methanol in dichloromethane as eluent to afford the product as an oil. Yield 0.2g Yield: 39.8%. The hydrochloride salt was prepared by the addition of molar quantity of ethereal hydrochloride to the ethanolic solution of free base and the obtained solid was collected by filtration m.pt 213-216° C.

MS m/z : 430 (MH^+)

IR (KBr cm^{-1}) : 1698 (C=O)

^1H NMR (300 MHz, $CDCl_3$) δ: 1.43 (6H, d), 1.79-1.83 (4H, m), 2.06-2.37 (4H, m), 2.91 (2H, bs), 3.11-3.94 (12H, m), 4.19 (1H, bs), 4.64-4.68 (1H, m), 6.92-7.16 (4H, m).

An illustrative list of the compounds of the invention which were synthesised by the above method is given below:

2-[3-{4-(2-Ethoxyphenyl) piperazin-1-yl}propyl]-5-chloro-6-hydroxy-3a,4,5,6,7,7a-hexahydro-1H-isoindole-1,3 (2H)-dione hydrochloride; m.p. 190-194° C,

2-[3-{4-(2-Ethoxyphenyl) piperazin-1-yl} propyl]-5-hydroxy-3a,4,5,6,7,7a-hexahydro-1H-isoindole-1,3 (2H)-dione hydrochloride; m.p. 210-213° C,

2-[3-{4-(2-Isopropoxyphenyl) piperazin-1-yl} propyl]-5-chloro-6-hydroxy-3a,4,5,6,7,7a-hexahydro-1H-isoindole-1,3 (2H)-dione hydrochloride; m.p. 160-164°C,

2-[3-{4-(2-(2,2,2-Trifluoroethoxy)phenyl)piperazin-1-yl}propyl]-5,6-epoxy-3a,4,5,6,7,7a-hexahydro-1H-isoindole-1,3(2H)-dione; m.p. oil,

2-[3-{4-(2-(2,2,2-Trifluoroethoxy)phenyl)piperazin-1-yl}propyl]-5-hydroxy-3a,4,5,6,7,7a-hexahydro-1H-isoindole-1,3(2H)-dione hydrochloride; m.p. 183-186° C.

EXAMPLE 5
(Scheme V)

Preparation of 2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}propyl]-5,6-dihydroxy-3a,4,5,6,7,7a-hexhydro-1H-isoindole-1,3 (2H)-dione hydrochloride

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}propyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione hydrochloride (1.8g, 4mmol), prepared using the procedure described in Example-1, was dissolved in ethanol (36 ml) and cooled to 0-5° C.

Aqueous sodium hydroxide solution (0.16g in 5 ml, 4mmol) was added followed by addition of aqueous solution of potassium permanganate (0.76g, 4.8 mmol) at 0-5° C and stirred for 4 hours at the same temperature. After the reaction was over, the precipitated maganese dioxide was filtered, washed with dichloromethane (25 ml). The solvent was removed under reduced pressure, water (50 ml) was added and extracted with dichloromethane (2x50 ml). The organic phase was dried over anhydrous sodium sulphate, concentrated *in vacuo* and the residue thus obtained was purified by chromatography on silica gel using 10% methanol in dichloromethane as eluent to afford 0.55g (30.7%) of the product.

The hydrochloride salt of the title compound was prepared in quantitative yield by the addition of molar quantity of ethanolic hydrogen chloride solution to a ethanolic solution of free base and the resultant precipitate was collected by filtration;

m.p. 213-216°C

MS m/z : 446.3 (MH^+)
IRKBrcm-1: 1693.4 (x=0)

1HNMR (300 MHz, DMSO-d_6) δ:1.27 (6H, d), 1.66-1.70 (2H, m), 1.89-1.93 (4H, m), 2.93-3.16 (8H, m), 3.36-3.50 (8H, m), 4.57-4.65 (1H, m), 6.83-6.98 (4H, m)

An illustrative list of the compounds of the invention which were synthesised by the above method is given below:

2-[3-{4-(2-Ethoxyphenyl)piperazin-1-yl}propyl]-5,6-dihydroxy-3a,4,5,6,7,7a-hexahydro-1H-isoindole-1,3 (2H)-dione ; m.p. low melting semisolid,

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}propyl]-5,6-dihydroxy-3a,4,5,6,7,7a-hexahydro-1H-isoindole-1,3 (2H)-dione ; m.p. low melting semisolid,

2-[3-{4-(2-Ethoxyphenyl)piperazin-1-yl}propyl]-5,6-dihydroxy-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione hydrochloride; m.p. 222-225° C,

EXAMPLE 6
(Scheme VI)

Preparation of 2-[3-{4-(2-Ethoxyphenyl)piperazin-1-yl,1-N-oxide}propyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione.

2-[3-{4-(2-Ethoxyphenyl)piperazin-1-yl}propyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione (0.5 g, 1.26 mmol), prepared by the method as described in Example-I, was dissolved in dichloromethane (10 ml) and cooled to 0° C. A solution of m-chloroperbenzoic acid (0.217g, 1.26 mmol) in dichloromethane (5 ml) was then added slowly over a period of 10 minutes, and the reaction mixture was further stirred for 2 hours at 0-5° C and then left at room temperature overnight. After the reaction was over, it was poured into aqueous potassium carbonate solution (5%, 30 ml). The organic layer was separated, dried over sodium sulphate, and concentrated. The crude product was purified by chromatography on silica gel, using 10% methanol in dichloromethane as eluent to afford the title compound Yield 0.11g (21%) m.p. 75-80° C,

IRKBrcm^{-1} : 1694 (c=0)
MS m/z: 414 (MH^+)

^{1}HNMR (300 MHz, $CDCl_3$) δ: 1.44 (3H, t), 2.24-2.65 (6H, m), 3.11 (2H, t), 3.22-3.23 (4H, m), 3.29-3.44 (4H, m), 3.62-3.66 (4H, m), 4.06-4.09 (2H, q), 5.90-5.92 (2H, m), 6.85-7.02 (4H, m).

An illustrative list of the compounds of the invention which were synthesised by the above method is given below:

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl, 1-N-oxide}propyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione; m.p. 85-89° C,

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl,1,4-N,N-dioxide}propyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3-(2H)-dione; m.p. 178-180° C,

2-[3-{4-(2-Ethoxyphenyl)piperazin-1-yl,1,4-N,N-dioxide}propyl]-3a-4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione; m.p. 176-178° C,

2-[3-{4-(2-Hydroxyphenyl)piperazin-1-yl, 1-N-oxide}propyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione; m.p. 198-202° C,

1-[4-(2-Methoxyphenyl)piperazin-1-yl-4-N-oxide]-3-(2,6-dioxopiperidin-1-yl]propane; m.p. 190-194° C,

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl, 1-N-oxide}propyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione,

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl, 1-N-oxide}propyl]-2-hydroxypropyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione hydrochloride; m.p. 191-197° C,

1-[4-(2-Methoxyphenyl)piperazin-1-yl,1-N-oxide]-3-(2,6-dioxopiperidin-1-yl]-2-hydroxypropane; m.p. 178-182 C,

1-[4-(2-Hydroxyphenyl)piperazin-1-yl,1-N-oxide]-3-(2,6-dioxopiperidin-1-yl]propane; m.p. 186-190° C.

EXAMPLE 7
(Scheme VII)

Preparation of 2-[[N-{N'-(2-Isopropoxyphenyl)aminoethyl}aminopropyl] -3a,4, 7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride

A mixture of 1-(3-bromopropyl)-*cis*-3a, 4,7,7a-tetrahydrophthalimide (6.0g, 22 mmol), N- (*β*-aminoethyl)-*o*-isopropoxy aniline (4.27g, 22 mmol) and potassium carbonate (3.0g, 22 mmol) in N, N-dimethyl formamide (30 ml) was stirred at 30-40° C for about 24 hrs. After the reaction was over, reaction mixture was poured in cold water (300 ml) and extracted with ethyl acetate (2x100 ml). The combined ethyl acetate layer was washed with water (2x100 ml), dried over anhydrous sodium sulphate, and concentrated *in vacuo* to yield crude oil. The crude product was purified by column chromatography on silica gel, using dichloromethane/methanol (9/1, v/v) as eluent to afford the desired compound as an oil. The compound thus obtained was converted into its hydrochloride salt as off white solid m. p. 168-170° C. Yield 5.5 g (64%)

MS m/z 386.5 (MH^+),
IR KBr cm^{-1} 1702.9 (C=O).

^1H NMR ($CDCl_3$) δ: 1.37-1.39 (6H, d), 2.14-2.19 (4H, m), 2.53-2.58 (2H, b s), 3.11 (2H, b s), 3.25 (2H, b s), 3.47-3.49 (2H, m), 3.76 (2H, m), 4.53-4.62 (1H, m), 5.85-5.89 (2H, m), 6.83-6.95 (4H, m).

An illustrative list of the compounds of the invention which were synthesised by the above method is given below:

1-[N-(β-aminoethyl)-2-methoxyaniline]-3-[2,6-dioxopiperidin-1-yl]propane hydrochloride ; m.p. 198-201° C.

EXAMPLE 8
(Scheme VIII)

Preparation of 2-[[N-{N'-(2-Isopropoxyphenyl) aminoethyl}hydroxyethyl] aminopropyl]- 3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride;

The compound resulting from Example 7 (1g, 2.6 mmol) was dissolved in N, N-dimethylformamide (10 ml). To this solution chloroethanol (0.209g, 2.6 mmol) was added, followed by anhydrous potassium carbonate (0.36g, 2.6 mmol). The reaction mixture was heated to 120-124° C for 4 hrs. After the reaction was over, reaction mixture was poured into cold water (100 ml) and extracted with ethyl acetate (2x100 ml). The combined ethyl acetate layer was washed with water (2x100 ml) and dried over anhydrous sodium sulphate. The organic phase was concentrated *in vacuo* and purified by column chromatography on silica gel, using dichloromethane/methanol (90/10, v/v) as eluent to give the desired compound as an oil. The compound thus obtained was converted into its hydrochloride salt as off white solid; m. p. 135-138° C

Yield 0.75g (68%)

MS m/z 429.9 (MH^+),
IR KBr cm^{-1} 1692.2 (C=O)., 3417 (OH)

^1H NMR ($CDCl_3$) δ: 1.34-1.36 (6H, d), 2.16-2.22 (4H, m), 2.57-2.62 (2H, b d), 3.15-3.21 (4H, m), 3.27-3.31 (4H, m), 3.54-3.58 (2H, m), 3.77-3.79 (2H, m), 3.98 (2H, b s), 4.51-4.59 (1H, m), 5.89 (2H, b s), 6.61-6.73 (2H, m), 6.78-6.88 (2H, m).

An illustrative list of the compounds of the invention which were synthesised by the above method is given below:

2-[N-{N'-(2-Isopropoxyphenyl)aminoethyl}acetylaminopropyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione hydrochloride; m.p. 134-137° C,

2-[N-{N'-(2-Isopropoxyphenyl)acetylaminoethyl}aminopropyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione hydrochloride; m.p. 157-160° C,

2-[N-{N'-(2-Isopropoxyphenyl)aminoethyl}acetaldehyde-aminopropyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione,

2-[N-{N'-(2-Isopropoxyphenyl)aminoethyl}aminopropyl-N-N'-(bishydroxyethyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione,

2-[N-{N'-(2-Isopropoxyphenyl)aminoethyl}ethylacetate-aminopropyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione,

2-[N-{N'-(2-Isopropoxyphenyl)aminoethyl}formylaminopropyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione,

2-[3-{4-(2-Isopropoxyphenyl)piperazin-3-oxo-1-yl}propyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione,

1-[N, N-{N'-(2-Methoxyphenyl)aminoethyl}-2-hydroxyethyl]-3-(2,6-dioxopiperidin-1-yl]aminopropane hydrochloride; m.p. 175-178° C,

2-[3-{3-(2-Isopropoxyphenyl)imidazolidon-1-yl}propyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione,

2-[N-{N'-(2-Isopropoxyphenyl)aminoethyl}aminopropyl-N'-(β-hydroxyethyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione hydrochloride,

2-[N-{N'-(2-Isopropoxyphenyl)aminoethyl}acetylaminopropyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione.

EXAMPLE 9
(Scheme - IX)

Preparation of 2-[3-{4-(2-Isopropoxyphenyl)-2,3-dioxopiperazin-1-yl}-propyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione;

To a solution of Compound No. 42 (Example 7) (0.5 g, 1.298 mmol) in dichloromethane was added triethylamine (0.197 g, 1.97 mmol) and the resulting reaction mixture was cooled to -10° C; followed by dropwise addition of oxalyl chloride (0.247 g, 1.94 mmol). The reaction temperature was raised to room temperature and stirred for 1 hr. After completion of the reaction, it was quenced by adding water (10 ml) to it, and then it was extracted with ethyl acetate (2x10 ml).The combined organic layer was concentrated under reduced pressure to yield a crude oil. The crude product was purified by column chromatography on silica gel (60-120 mesh), using dichloromethane/methanol (9.8:0.2) as an eluent to afford the product as an oil.

MS m/z 440 (MH^+),

^1H NMR ($CDCl_3$) δ: 1.32-1.34 (6H, d), 1.89-1.94 (2H, m), 2.17-2.25 (2H, m), 2.60-2.63 (2H, m), 3.10-3.12 (2H, m), 3.48-3.57 (4H, m), 3.64-3.67 (2H, m), 3.80-3.82 (2H, m), 4.56-4.60 (1H, m), 5.83-5.92 (2H, m), 6.87-6.98 (4H, m).

EXAMPLE 10
(Scheme X)

Preparation of 2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}propyl]-4,7-diacetoxy-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione hydrochloride;

A mixture of 1-amino-3-[4-(2-isopropoxyphenyl)piperazin-1-yl]propane(1g,3.6 mmol) and maleic anhydride (0.36 g,3.6 mmol) was refluxed in toluene for 3 hrs with azeotropic removal of water . After the completion of the reaction, the solvent was removed under reduced pressure and the residue thus obtained was column chromatographed to afford an oily product (yield 0.82 g, intermediate) The mixture of this intermediate (0.8, 2.24 mmol) and 1,4-diacetoxy-1,3-butadiene (0.38 g, 2.24 mmol) were refluxed in toluene for 8 hrs. After completion of the reaction, the solvent was removed under reduced pressure. The crude product was purified by chromatography using dichloromethane methanol (9.9:0.1) as eluent. The oily product thus obtained was finally converted into its hydrochloride salt (m.p. 176-177° C).

IR (KBr cm-1) : 1703.2 (C=O), 1741.3 (C=O).

MS m/z : 528 (MH^+)

^{1}H NMR ($CDCl_3$) δ : 1.35-1.37 (6H,d), 2.13 (6H,s), 2.20-2.23(2H,m),3.01(4H,br s), 3.52-3.56 (6H,m),3.61-3.63(2H,m),3.68-3.69(2H,m),4.57-4.61(1H,m),5.42-5.43(2H,m), 6.16 (2H,m),6.85-6.90(3H,m),6.99-7.02(1H,m).

An illustrative list of the compounds of the invention which were synthesised by the above method is given below:

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}propyl]-5,6-dimethoxy-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione hydrochloride;m.p. 153-155° C,

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}propyl]-4,7-diphenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione hydrochloride;m.p. 193-194° C,

2-[3-{4-(2-methoxyphenyl)piperazin-1-yl}propyl]-4,7-diphenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3 (2H)-dione hydrochloride;m.p. 224-225° C,

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}propyl]-4-hydroxy-3a,4,5,6,7,7a-hexahydro-1H-isoindole-1,3 (2H)-dione hydrochloride;m.p. 163-165° C,

2-[3-{4-(2-Isopropoxyphenyl)piperazin-1-yl}propyl]-5,6-dimethoxy-3a,4,5,6,7,7a-hexahydro-1H-isoindole-1,3 (2H)-dione hydrochloride;m.p. 143-146° C.

Pharmacological Testing Results

Receptor Binding Assays

Receptor binding assays were performed using native α-adrenoceptors. The affinity of different compounds for α_{1A} and α_{1B} adrenoceptor subtypes was evaluated by studying their ability to displace specific [^{3}H] prazosin binding from the membranes of rat submaxillary and liver respectively (Michel *et al.*, Br J Pharmacol, 1989; 98:883). The binding assays were performed according to U'Prichard et al. (Eur J Pharmacol, 1978; 50:87 with minor modifications.

Submaxillary glands were isolated immediately after sacrifice. The liver was perfused with buffer (Tris HCl 50 mM, NaCl 100mM, 10 mM EDTA pH 7.4). The tissues were homogenised in 10 volumes of buffer (Tris HCl 50 mM, NaCl 100mM, 10 mM EDTA pH 7.4). The homogenate was filtered through two layers of wet gauge and filtrate was centrifuged at 500 g for 10 min. The supernatant was subsequently centrifuged at 40,000 g for 45 min. The pellet thus obtained was resuspended in the same volume of assay buffer (Tris HCl 50 mM, 5 mM EDTA pH 7.4) and was stored at -70° C until the time of assay.

The membrane homogenates (150-250 µg protein) were incubated in 250 µl of assay buffer (Tris HCl 50 mM, EDTA 5 mM, pH 7.4) at 24-25° C for 1 hour. Non specific binding was determined in the presence of 300 nM prazosin. The incubation was terminated by vacuum filtration over GF/B fibre filters. The filters were then washed with ice cold 50mM Tris HCl buffer (pH 7.4). The filtermats were dried and bound radioactivity retained on filters was counted. The IC_{50} and Kd were estimated by using the non-linear curve-fitting program using G Pad Prism software. The value of inhibition constant Ki was calculated from competitive binding studies by using Cheng & Prusoff equation (Cheng & Prusoff, Biochem Pharmacol, 1973,22: 3099-3108), $Ki = IC_{50}/(1+L/Kd)$ where L is the concentration of [^{3}H] prazosin used in the particular experiment (Table I).

In Vitro Functional Studies

In order to study selectivity of action of these compounds towards different α-adrenoceptor subtypes, the ability of these compounds to antagonise (α_{1D}) prostate (α_{1A}) and spleen (α_{1B}) was studied. Aorta and spleen tissues were isolated from urethane anaesthetized (1.5 g/kg) male wister rats. Isolated tissues were mounted in organ bath containing Krebs Henseleit buffer of the following composition (mM): NaCl 118; KCl 4.7; $CaCl_2$ 2.5; $MgSO_4$ $7H_2O$ 1.2; $NaHCO_3$ 25; KH_2PO_4 1.2; glucose 11.5. Buffer was maintained at 37° C and aereated with a mixture of 95% O_2 and 5% CO_2. A resting tension of 2g (aorta) or 1g (spleen and prostate) was applied to tissues. Contractile response was monitored using a force displacement transducer and recorded on chart recorders. Tissues were allowed to equilibrate for 2 hours. At the end of equilibration period, concentration response curves to norepinephrine (aorta) and phenylepinephrine (spleen and prostate) were obtained in the absence and presence of tested compound (at concentration of 0.1,1 and 10 mM). Antagonist affinity was calculated and expressed as pK_B values in Table II.

In Vivo Uroselectivity Study

In order to assess the uroselectivity in vivo, the effects of these compounds were studied on mean arterial pressure (MAP) and intraurethral pressure (IUP) in conscious beagle dogs as per the method of Brune et al. (Pharmacol., 1996, 53:356). Briefly, male dogs were instrumented for chronic continuous measurement of arterial blood pressure by implanting a telemetry transmitter (TL11M2-D70-PCT, Data Sci. International, St. Paul, MN USA) into the femoral artery, two weeks prior to the study. During the recovery period, the animal was acclimatized to stay in the sling restraint. On the day of testing, overnight fasted animal was placed in the sling restraint. A Swan-Ganz. Balloon tipped catheter was introduced into the urethra at the level of prostate and the balloon was inflated (Brune. et. al. 1996). After recording the base line readings, effect of 16 μg/kg, phenylephrine (i.v.) on MAP and IUP was recorded. The response of phenylephrine to MAP and IUP were recorded at 0.5, 1, 2, 3, 4, 6, 9 and 24 hours after the oral administration of vehicle or the test drug. The changes in MAP were recorded on line using Dataquest Software (Data

Sci. International, St. Paul, MN. USA). The change in phenylephrine response on MAP and IUP administration after the test drug administration was calculated as percent change of that of control values. Area under curve was calculated, and the ratio of the values for MAP and IUP was used for calculating the uroselectivity (Table III).

Table I: Radioligand Binding Studies:

Affinity of compounds for Alpha-1 Adrenoceptor Subtypes

Compound No.	α_{1A} (Rat Submaxillary)	α_{1B} (Rat Liver)	α_{1B}/α_{1A}
01	8.55	80	9
02	0.17	27	159
03	0.26	47	181
04	22	>1000	>45
05	70	1376	20
06	38	263	7
07	0.56	106	189
08	6.6	4767	722
09	1068	>1000	
10	>1000	>1000	
11	6.4	191	30
12	1.7	118	69
13	0.36	85	236
14	49	504	10
15	35	346	10
16	19	267	14
17	1.6	80	50
18	1.5	97	65
19	0.23	104	452
20	0.28	92	328
21	3.4	643	189
22	1587	1093	0.7
23	0.98	127	130
24	5.9	495	84
25	0.86	173	201
26	8.83	2090	237
27	306	>5000	16
28	0.24	41	171
29	2.8	238	85
30	1.7	393	231
31	2.3	91	40

Compound No.	α_{1A} (Rat Submaxillary)	α_{1B} (Rat Liver)	α_{1B}/α_{1A}
32	0.18	51	283
33	0.24	34	142
34	1.95	311	159
35	38	582	15
36	11	571	52
37	462	>1000	>2
38	141	760	5
39	6.9	1377	200
40	0.82	143	174
41	0.3	105	350
42	19	781	41
43	0.5	50	100
44	594	1738	3
45	8.6	120	14
46	379	>1000	>3
47	299	>1000	>3
48	91	>1000	>11
49	>1000	>1000	1
50	47	>1000	>21
51	662	>15000	>23
52	351	>15000	>43
53	74	>15000	>203
54	7286	>15000	>2
55	72	3637	51
56	>100	992	>10
57	>1000	>1000	1
58	160	>1000	10
59	2.3	48	21
60	1.2	142	118
61	0.93	29	31
62	>1000	>1000	1
63	>100	>1000	>10
64	28.5	870	31
65	>1000	>1000	1
66	5.2	167	32
67	189	>10000	>53
68	228.5	>10000	>44
69	7160	>10000	>10
70	6754	4920	0.7
71	>1000	>10000	1
72	0.54	142	263
73	8.45	192	23

Compound No.	α_{1A} (Rat Submaxillary)	α_{1B} (Rat Liver)	α_{1B}/α_{1A}
74	202	>15000	>74
75	2.3	71	31
76	1.4	192	137
77	485	916	1.9
78	322	334	1

Table II: In Vitro Functional Assays

Compound No.	α Adrenoceptor Subtype (pK_B)			Selectivity	
	α_{1A}	α_{1B}	α_{1D}	α_{1B}/α_{1A}	α_{1D}/α_{1A}
01	8	7.42	7.92	3.8	1.2
02	9.74	8.89	10.5	7.07	0.17
03	9.41	9.56	9.83	0.7	0.38
04	8.61	8.15	7.09	2.9	33
06	8.18		8.43		0.56
07	8.91	7.8	8.64	13	1.9
08	8.38	8.99	7.66	0.24	5.24
09	8.15	7.63	7	3.3	14
10	8.83	7.73	7.23	13	40
11	8.14	9.12	8.43	0.1	0.5
12	8.78	7	8.16	60	4.2
13	8.49	7.26	8.64	17	0.7
17	9.54	7	9.07	347	3.9
18	9.37		9.24		1.3
19	9.1	7.16	8.57	87	3.4
20	9.37	6.99	8.97	240	2.5
21	8.33	7.15	7.61	15	5.24
23	8.83	8.13	8.08	5	5.6
25	8.34	7	8.37	22	0.93
26	8.8		6.78		105
28	9.01	7.36	8.85	45	1.4
29	9.64		7.99		45
30	8.78		8.06		5.2
31	8.84		8.32		3.3
32	9.17		7.8		23
33	9.22	7.96	8.8	18	2.6
34	8.9		7.72		15
40	9.47		8.82		4.5
41	9.29	7.17	8.61	132	4.8
43	8.77	7.9	9.13	7.4	0.43
60	9.44		8.19		18

Table III: In Vivo Uroselectivity Studies in Conscious Beagle Dogs

Compound No.	Dose (µg/kg)	Route	Area Under Curve		Uroselectivity Ratio
			MAP	IUP	IUP/MAP
23	30	p.o	95	524	5.5
Tamsulosin (SR)	3	p.o	868	592	1.47

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.